PROCESSING OF STIMULUS REPETITION AND CHANGE IN THE SOMATOSENSORY SYSTEM: RECORDINGS OF ELECTRICAL AND MAGNETIC BRAIN RESPONSES

Doctoral Dissertation

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ABSTRACT

PROCESSING OF STIMULUS REPETITION AND CHANGE IN THE SOMATOSENSORY SYSTEM: RECORDINGS OF ELECTRICAL AND MAGNETIC BRAIN RESPONSES

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In the present work, effects of stimulus repetition and change in a continuous stimulus stream on the processing of somatosensory information in the human brain were studied. Human scalp-recorded somatosensory event-related potentials (ERPs) and magnetoencephalographic (MEG) responses rapidly diminished with stimulus repetition when mechanical or electric stimuli were applied to fingers. On the contrary, when the ERPs and multi-unit activity (MUA) were directly recorded from the primary (SI) and secondary (SII) somatosensory cortices in a monkey, there was no marked decrement in the somatosensory responses as a function of stimulus repetition. These results suggest that this rate effect is not due to the response diminution in the SI and SII cortices. Obviously the responses to the first stimulus after a long "silent" period are enhanced due to unspecific initial orientation, originating in more broadly distributed and/or deeper neural structures, perhaps in the prefrontal cortices. With fast repetition rates not only the late unspecific but also some early specific somatosensory ERPs were diminished in amplitude. The fast decrease of the ERPs as a function of stimulus repetition is mainly due to the disappearance of the orientation effect and with faster repetition rates additively due to stimulus specific refractoriness.

A sudden infrequent change in the continuous stimulus stream also enhanced somatosensory MEG responses to electric stimuli applied to different fingers. These responses were quite similar to those elicited by the deviant stimuli alone when the frequent standard stimuli were omitted. This enhancement was obviously due to the release from refractoriness because the neural structures generating the responses to the infrequent deviants had more time to recover from the refractoriness than the respective structures for the standards. Infrequent deviant mechanical stimuli among frequent standard stimuli also enhanced somatosensory ERPs and, in addition, they elicited a new negative wave which did not occur in the deviants-alone condition. This extra negativity could be recorded to deviations in the stimulation site and in the frequency of the vibratory stimuli. This response is probably a somatosensory analogue of the auditory mismatch negativity (MMN) which has been suggested to reflect a neural mismatch process between the sensory input and the sensory memory trace.

1. INTRODUCTION

1.1. Somatosensory event-related potentials (ERPs)

Somatosensory ERPs are time-locked brain responses to somatosensory stimuli. Responses elicited by single stimuli are quite small (< 20 μV) compared with deflections of the background electroencephalogram (EEG) (50 - 100 μV). Therefore, ERPs to single stimuli are hardly distinguished from the background brain activity unrelated to the stimulus processing. ERPs can be extracted from the background activity by averaging post-stimulus EEG epochs. In this procedure EEG deflections not synchronized to stimuli are cancelled out and an ERP, i.e., voltage changes synchronized to stimuli, is obtained.

Electric stimuli are most commonly used to elicit somatosensory ERPs, especially for diagnostic purposes to expose possible peripheral or central neurological abnormalities (for a review, Desmedt, 1988). This kind of stimulation has some benefits. It bypasses sensory receptors and directly stimulates afferent nerves. Therefore, temporal dispersion in afferent volleys arriving at the cortex is small and elicits distinct ERPs. However, electric pulses stimulate all nerves and are in this sense unspecific. A futher disadvantage of electric stimuli is that they often cause large muscle artifacts (Bennett and Janetta, 1980; Findler and Feinsod, 1982; Leandri *et al.*, 1987). By using more natural mechanical stimuli, it is possible to selectively stimulate different submodality channels (different receptor systems; see Bolanowski *et al.*, 1988; Vallbo and Johansson, 1984) without the afore-mentioned disadvantages. For instance, by applying low (< 80 Hz) and high frequency (> 80 Hz) mechanical vibrations to the skin, it is possible to study how the rapidly adapting (RAI) and Pacinian afferent (RAII) systems contribute to the exegenous (stimulus-specific) somatosensory ERPs.

The neural origins[1] of the early (deflections with latencies $\leq$ 50 ms) somatosensory ERPs are rather wellknown (Allison *et al.*, 1980; 1989a; 1991; Baumgartner *et al.*, 1991; Desmedt, 1988; Desmedt and Tomberg, 1989; Forss *et al.*, 1994b; Garcia-Larrea *et al.*, 1991; Ibáñez *et al.*, 1995; Mauguière *et al.*, 1983; 1997a; Nicholson Peterson *et al.*, 1995; Noël and Desmedt, 1975; Rossini *et al.*, 1989; Slimp *et al.*, 1986; Wood *et al.*, 1985). Early somatosensory ERPs are rather resistant to psychological manipulations (cognitive factors) and to pharmacological interventions (Clark and Rosner, 1973; Hume, 1979). These early components depend mainly on stimulus parameters, in other words, they are obligatory exegenously determined components. However, some studies have shown that also all early cortical components, except for the first cortical N20 component (a negative ERP deflection peaking at 20 ms from stimulus onset), are sensitive to cognitive factors, for example, to the direction of attention (Desmedt and Brunko, 1980; Desmedt and Tomberg, 1989; Desmedt *et al.*, 1987b; Josiassen *et al.*, 1982; Tomberg and Desmedt, 1996; Tomberg *et al.*, 1989). Desmedt and Tomberg (1991) proposed, however, that these enhancements in early somatosensory ERPs with attention are too early to be elicited by real post-stimulus cognitive processing, but they are manifestations of the selective priming of the cortical analyzers preset by instructions (cf., Drevets *et al.*, 1995; Näätänen, 1975; Roland, 1981). This intepretation is also concordant with the intracortical recordings in monkeys according to which the multi-unit (MUA) responses to vibration bursts were enhanced by attention in the SII but not SI cortices (Hyvärinen, 1980; 1982; Poranen and Hyvärinen, 1982).

Late ERPs (latencies $\geq$ 100 ms) are more susceptible to experimental conditions and, especially, to psychological manipulations. Therefore, they are often called endogenous potentials (see Picton and Hillyard, 1988). The division of ERPs into exegenous and endogenous potentials is not so simple, however, because, as already mentioned, the early components are susceptible to cognitive factors, too, and, on the other hand, most of the late components, as the auditory N1 (or N100) (see Näätänen, 1987; Näätänen and Picton, 1987) and somatosensory N140 (García-Larrea *et al.*, 1995), include several subcomponents of both exegenous and endogenous. In the present Studies I-IV, only the exogenous P50 and later somatosensory cognitive ERPs, especially, P100, N140, N250, P300, and the possible somatosensory mismatch-negativity (MMN) are discussed.[2]

[1] Neural origins of somatosensory ERPs will be discussed in greater detail in chapter 5.3.

[2] In the literature, the auditory and visual ERP deflections, especially the late deflections, are ordinarily named by using the abbreviations N1, P2, P3 instead of N100, P200, P300. The somatosensory deflections, on the other hand, are, usally,named by using the long markings P50, P100, N140, etc. This custom is followed in this work, too.

1.2. Effects of stimulus repetition on ERPs

The late ERPs are sensitive to stimulus repetition. Especially, the vertex negativity (N1) and the N1-P2 amplitude (difference between the N1 and P2 peak amplitudes) as well as the P3 diminish with stimulus repetition (Picton *et al.*, 1976). The late ERPs to the first stimulus in a train are large in amplitude and diminish rapidly with repetition, reaching a low asymptotic level after a few stimulus presentations. The decrease of ERPs is faster and more pronounced with faster stimulus presentation rates (Angel *et al.*, 1985; Fruhstorfer *et al.*, 1970). The ERP components differ from each other in sensitivity to this rate effect. In general, the longer the latency of a component, the more sensitive it is to the rate effect. For example, in the work of Tomberg et al. (1989), the somatosensory N140 totally dissappeared when the interstimulus interval (ISI) was shortened from 2500 ms to 1400 ms. Simultaneously also the early components decreased in amplitude but were still clearly discernible when the ISI was 450 ms. Only the first somatosensory cortical component N20 did not change with these ISIs.

Decrement in ERPs with stimulus repetition is not a consequence of sensory adaptation or fatigue in the receptors afferent pathway (except with very fast stimulus rates, hundreds stimuli/s) for the first cortical response is fully recovered with ISIs longer than 200 ms (Huttunen and Homberg, 1991; McLaughlin and Kelly, 1993). This is concordant with the results of Ibáñez et al. (1995) according to which the regional cerebral blood flow (rCBF) increases in the primary somatosensory area (SI) linearly with the stimulus-presentation frequency up to the 4 Hz but not with faster rates ($\geq$8 Hz). Obviously, the primary cortical areas, in spite of stimulus repetition, receive accurate stimulus information which is available there some time for further processing if needed. This is in a good agreement with the fact that the subjective intesities of the evoked sensations do not depend on changes in ERPs with stimulus repetition (Chapman *et al.*, 1981). The amplitude decrease of the ERPs begins with too long ISIs to be explainable by refractory periods in simple cellular mechanisms (Näätänen and Picton, 1987). In the somatosensory systems, the ERP amplitude decrement is probably caused by complex inhibitory mechanisms within the parietal cortex that reduce the excitatory postsynaptic potentials (see Whitsel *et al.*, 1989; 1991).

Late ERPs increase in amplitude with the prolongation of ISI. Auditory N1, P2, and P3 and somatosensory N140, P200, and P300 components linearly increase in amplitude as a function of the ISI (Miltner *et al.*, 1991). The full recovery of the N1 requires about 10 s (Davis *et al.*, 1966; Fruhstorfer *et al.*, 1970; Näätänen, 1988; Ritter *et al.*, 1968). Interestingly, also the human auditory sensory memory trace persists about 10 s (Cowan, 1984; 1988; Cowan *et al.*, 1993; Lu *et al.*, 1992; Sams *et al.*, 1993). The enhancement of the late ERPs, especially the N1 and P3 components, to the first stimulus is often associated to the initial orienting reaction (I-OR) (Kenemans *et al.*, 1989; Näätänen and Gaillard, 1983). The very first stimulus in any series after a long 'silent' period probably catches attention and it elicits a large N1 which is followed by the large P3 (P3a), indicating the occurrence of the attention switch (Alho *et al.*, 1998;Escera *et al.*, in press; Snyder and Hillyard, 1976; Squires *et al.*, 1975), and then the full-scale classical orienting reaction (OR) (see Sokolov, 1975) occurs with its autonomic-nervous system responses (Lyytinen *et al.*, 1992; Lyytinen and Näätänen, 1987).

1.3. Effects of stimulus change on ERPs

In the auditory system, an occasional change in a continuous flow of stimuli elicits a negative shift in ERP beginning at about 100 ms and lasting 100-200 ms. This mismatch negativity (MMN) reflects the detection of stimulus change in the nervous system (Näätänen *et al.*, 1978). This "enhancement" of negativity resembles the changes in ERPs to the first stimulus in stimulus series or to deviant stimuli presented rarely alone without standards (cf. for example Fruhstorfer *et al.*, 1970 and Näätänen *et al.*, 1989). Attention or change in the direction of attention is an essential part in the OR. Any supraliminal change in auditory stimulus trains elicits an MMN (see for reviews Näätänen, 1990; 1992; Näätänen and Alho, 1995) and it can trigger the change-orienting response (C-OR) (Näätänen and Gaillard, 1983), but it does not necessarily do so (Lyytinen *et al.*, 1992). The MMN is independent of attention and is elicited irrespective of whether the subject (S) is attending or ignoring the deviant stimuli (Alho *et al.*, 1992; Näätänen, 1986; Näätänen *et al.*, 1978; 1993; Paavilainen *et al.*, 1993). Some studies have, however, shown that attention could have effect on the MMN (Alho *et al.*, 1992; Paavilainen *et al.*, 1993; Trejo *et al.*, 1995; Woldorff *et al.*, 1991) The mismatch process is an essential prerequisite for the C-OR. However, the stimulus change per se is not sufficient to

elicit the classical OR, but the stimulus deviation should be somehow significant or novel for S to trigger the full-scale OR (see Bernstein, 1979; Kenemans *et al*., 1989; Maltzman, 1979; Näätänen, 1986; Näätänen and Gaillard, 1983; O'Gorman, 1979; Öhman, 1979; Siddle and Spinks, 1979; Sokolov, 1975) .

In auditory ERPs, the responses to either the first stimuli in stimulus trains or to deviants among standards are enhanced compared with the responses elicited by the other subsequent or standard stimuli in the train, respectively. The initial response is mainly unspecific and is elicited by any first stimulus after a long silent period. On the contrary, an MMN is elicited by any supraliminal change (deviation from the standard stimulus) in auditory stimulus trains (Näätänen, 1992). Both responses rapidly attenuate with stimulus/deviant stimulus repetition (Sams *et al*., 1984). On the other hand, neither the first auditory stimulus in a sequence (Sams *et al*., 1985b) nor infrequent stimuli presented without standard stimuli elicit an MMN (Lounasmaa *et al*., 1989; Näätänen *et al*., 1989; Sams *et al*., 1985a). Within the somatosenory system, no analogous mismatch responses have been reported in previous studies.

In auditory passive or ignore oddball conditions, in which the attention of Ss is directed away from stimuli, rare deviant stimuli among frequently presented standard stimuli elicit an MMN. It is a second (N2 sometimes N2a) late negative deflection (after the N1) and overlapped by the N1. In active oddball situations, i.e. when Ss have to discriminate rare deviants among frequently presented standards, deviant (target) stimuli elicit an MMN and, in addition, a large negative N2b and positive P3 waves. N2b is peaking later than the MMN at 200-250 ms and is overlapped by it. In contrast to the MMN, the N2b and P3 are attention dependent, usually not occurring in ignore conditions (Näätänen *et al*., 1982; Ritter *et al*., 1992). N2b is usually followed by P3a, this association being quite strong (Courchesne *et al*., 1975; Loveless, 1986; Näätänen and Gaillard, 1983; Renault and Lesévre, 1978; 1979). N2b can, however, occur without P3a (Knight, 1990b; Ritter *et al*., 1992) for instance when discrimination was not successful (Sams *et al*., 1985b), and vice versa P3a can occur without N2b in ignore conditions when deviants suddenly catch attention (Sams *et al*., 1985b), suggesting different generators for these two components. Novak et al., (1992a) found a sequential relationship between MMN and N2-P3b; factors that increased the onset or peak latencies of MMN proportionately increased the latencies of the N2, P3b, and the reaction time (RT). The authors proposed that the automatic mismatch detection triggers the target recognition process indexed by N2, P3b, and behavioral responses of the subject (Novak *et al*., 1990; 1992a; 1992b;). This is supported by the results of Tiitinen et al., (1994) according to which the MMN peak latency and the RT change similarly with the magnitude of stimulus deviation. Probably N2b-P3(a/b) is related to conscious discrimination of change in a continous stimulus stream. However, it has also been proposed that temporal infrequency might be a more important factor than the deviance, because N2b could be elicited by isolated infrequent stimuli, too (Loveless, 1986; Näätänen and Gaillard, 1983). Thus, the deviance discrimination should not be necessary, but bare signal detection could be sufficient to elicit an N2b-P3 complex (Picton and Stuss, 1980).

In the somatosensory system, a comparable late negative-positive wave complex has been obtained as a response to electric (Ito *et al*., 1992; Josiassen *et al*., 1982) and tactile stimuli delivered to fingers (Kujala *et al*., 1995). In a multitude of studies, the somatosensory N250 (or N220 or N240) is clearly discernible but, unfortunately, neither reported nor analysed. The somatosensory N250-P300 seems to behave similarly to the auditory and visual N2b-P3, occurring in active oddball or discrimination situations. However, the determinants of the somatosensory N250-P300 are still rather deficiently known.

2. THE AIMS OF THE PRESENT STUDY

In the six studies to be reviewed here, two main problems are considered: (1) How do initial somatosensory ERPs and their magnetic counterparts change with stimulus repetition and what are the determinants of these changes? (2) How does a sudden change in a continuous flow of stimuli affect the somatosensory responses? In order to answer these questions, I used non-invasive EEG- (Studies I - III, V, and VI) and magnetoencepalographic (MEG-) recording (Studies II and IV) methods. In addition, in Study III I recorded intracortical ERPs and multiple-unit activity (MUA) in a monkey in order to determine the cerebral origin of the fast decrement of initial somatosensory ERPs with stimulus repetition.

3. METHODS

In the present Studies I-VI, three different methods of brain activity, EEG, MEG, and intracortical recordings, were used. Both EEG and MEG measure postsynaptic current flow in neurons located mainly in the cerebral cortex. The EEG and MEG are non-invasive methods with millisecond temporal resolution. The source location accuracy of both methods is also rather good. However, the MEG is more accurate, especially, in localization of fissural tangential current sources, on the other hand, the EEG "sees" more accurately the radial and deeper sources (for reviews, Hämäläinen *et al.*. 1993; Picton *et al.*, 1995; see also Anogianakis *et al.*, 1992). Because of these complementary properties, combined use of EEG and MEG is fruitful. The accurate current source localization requires a rather dense electrode montage and/or quite many channels in a SQUID magnetometer. It does not, however, completely solve the inverse problem. Therefore, in Study III, the intracortical ERPs were recorded in monkey to ascertain the neuronal origin of the fast decrement of the ERP responses as a function of repetition.

3.1. Human experiments

3.1.1. Subjects and experimental conditions

4-10 healthy volunteers (ages 18-42 years) participated in each experiment, in which EEG or MEG responses were recorded. The EEG Studies I, II, V, and VI were conducted in the Department of General Psychology at the University of Helsinki. In these experiments the S was sitting in a reclining chair in an electrically and acoustically shielded room, with their left hand supported by a vacuum cast on the exeperimental table. The MEG Studies II and IV were conducted in the magnetically shielded room of the Low Temperature Laboratory at the Helsinki University of Technology.

3.1.2. EEG Recordings

The EEG was recorded with Ag/AgCl electrodes from 3 contra- and 3 corresponding ipsilateral (stimuli to the left hand) locations, 5 cm anterior and 2 and 7 cm posterior to the approximate central sulcus at the lines from C4 and C3 to the nasion and inion, respectively, and at the vertex. In Study V, the electrodes were located at sites F3, F4, Cz, P3 and P4 and at sites C3' and C4' (2 cm behind approximated central sulci) of the 10-20 system (Jasper, 1958). The electro-oculographic (EOG) activity was recorded with an electrode attached above the right eye for eye-movement artefact rejection. The monopolar records were referred to the left mastoid, except for Study I in which they were referred to the nose. The recording bandwith was 0.1-100 Hz (-3dB) and the sampling rate was 250 Hz. The ERPs were computed separately by averaging EEG epochs starting 50 ms before and ending 400-500 ms after each stimulus onset for each subject, condition, and stimulus type. Frequencies higher than 40 Hz and lower than 0.1 Hz were digitally filtered out from the averaged ERPs. The mean amplitude over a 50-ms prestimulus period was used as a baseline for the amplitude measurement. EEG epochs with amplitudes exceeding 75 μV (or 120 μV in Study VI) were rejected from the analysis.

3.1.3. MEG Recordings

The MEG recordings were performed with a 7-channel first-order direct current superconducting quantum interference device (DC-SQUID) gradiometer (field sensitivity 5-6 fT/Hz) (for technical details, see Knuutila *et al*., 1987) from two optimal positions over the hemisphere contralateral to the stimulated hand for the measurement of activity in the primary (SI) and secondary (SII) somatosensory cortices. In this device, the pickup coil centers are separated by 36.5 mm, and they are arranged in a hexagonal array on a spherical surface (radius 125 mm). Some control experiments (in Study IV) were carried out also with a newer 24-channel SQUID-device (for technical details, see Kajola *et al*., 1990).

The recording passband was 0.05-500 Hz (high-pass roll-off 35 dB/decade and low-pass over 80 dB/decade). The mean amplitude over a 40-ms prestimulus period was used as the baseline for the amplitude measurement. Responses with amplitudes exceeding 150 μV in the simultaneously recorded vertical (electrodes over and below the right eye) EOG were rejected from the analysis.

3.1.4. Somatosensory stimulation

Mechanical pulses or bursts of vibration with different amplitudes and frequencies served as the stimuli in the EEG Studies I, III, V, and VI.

The mechanical stimuli were applied to the left middle finger (and to the thumb in Study III) by an electromechanical vibrator (Brüel & Kjaer 4810). The amplitudes and frequencies were measured with an accelerometer (Brüel & Kjaer 4339) and monitored with an oscilloscope.

In the MEG Studies II and IV, 0.3-ms constant-current pulses (Grass S88 stimulator, Grass SIU 4678 isolation unit, and Grass CCU 1A constant current unit) were used as stimuli. They were delivered to the volar skin of the left middle finger (Study II), and to the left middle finger and thumb (Study IV) via contact electrodes moistened with NaCl solution.

3.2. Animal experiment

In Study III, somatosensory ERPs and multiunit activity (MUA) were directly recorded from the cortex of a female monkey (*Macaca Arctoides*). This animal experiment was conducted in the electrically shielded room of the Neurophysiological Laboratory at the Department of Physiology, University of Helsinki.

In this experiment, the EEG and MUA were recorded with the same glass-coated semimicroelectrode with different bandwidths 1-1000 Hz and 300-3000 Hz, respectively. The recordings were referred to the metal ring screwed to the skull of the monkey (for more detailed description of intracortical recordings in monkeys, see Hämäläinen *et al.*, 1988). The recordings were obtained from both SI and SII cortices. Otherwise, the experimental paradigm and mechanical stimulation were the same as in the human Studies II and VI with short stimulus trains.

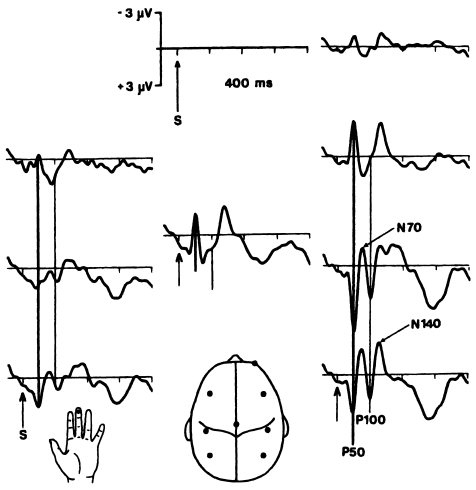

Fig. 1. *Somatosensory ERPs to single slow pulses of an individual subject at different locations over the right hemisphere contralateral to the stimulated hand, homologous sites over the ipsilateral (left) hemispere, and at the vertex (middle trace). Eye movements were recorded with the electrode positioned above the right eye (the upper trace on the right). The arrows indicate stimulus onset. The analysis period (450 ms) began 50 ms before the stimulus onset and ended 400 ms after it. The P50 (peaking at 45 ms for this particular subject) is marked by the thick vertical line on the contralateral traces. For the other traces the lines are drawn at the same latencies as contralaterally. The N70 and N140 peaks are also indicated by arrows on the contralateral traces. The insert, in which the Cz is located according to Jasper (1958), shows the approximate electrode locations with respect to the central sulcus. The stimulus site is shown by the dot in the middle finger of the left hand. Data of Study I.*

4. RESULTS

4.1. Human somatosensory ERPs to mechanical stimuli (Study I)

In Study I, ten healthy Ss (ages 20-35, 3 females) were instructed to read a book and to ignore mechanical stimuli. The stimuli were either low- (24 Hz) and high-frequency (240 Hz) single half-cycle sinusoid pulses, or low- and high-frequency 300-ms vibration bursts. The amplitude of low-frequency pulses (base-to-peak) and vibrations (peak-to-peak) was 1000 µm and 120µm for high-frequency stimuli, respectively. The stimuli were delivered to the tip of the left middle finger at a rate of 1 stimulus/1.5 s.

4.1.1. Contralateral P50 to mechanical pulses reverses its polarity at the central sulcus

Fig. 1 shows the average ERPs to low-frequency pulses from one subject. The first distinct response was an anteriorly negative, and centroposteriorly positive, deflection. It could be measured from all 10 subjects and it peaked over the scalp area contralateral to the stimulated hand at 50 $\pm$ 3 ms (mean $\pm$ standard error of mean) and at 49 $\pm$ 1 ms to the low- and high-frequency pulses,

respectively. The contralateral P50 showed a clear anterior-to-posterior polarity reversal, whereas it was hardly detectable over the scalp ipsilateral to the stimulation.

The P50 was followed by a contralateral posterior N70 (Fig. 1). It was largest at the middle and posterior locations on the contralateral hemisphere. It was more distinct for the low- than high-frequency pulses. It could be measured from 10 subjects to the low- (75 ± 2.8 ms) and from 6 subjects to the high-frequency pulses (75 ± 4.4 ms).

These two deflections were followed by a positive P100 peak, which was larger contra- than ipsilaterally. P100 was measurable from all 10 subjects, with the average peak latency 97 ± 3.6 ms contralaterally and 105 ± 5.6 ms ipsilaterally for the low-frequency pulses and 94 ± 4.4 ms and 98 ± 4.5 ms for the high-frequency pulses, respectively.

The N140 was contralaterally recorded to both the low- and high-frequency pulses. It was larger in amplitude in the posterior recording locations, and it was considerably larger to the high-frequency than to the low-frequency pulses. It could be measured from 6 subjects to the low-frequency pulses (143 ± 10.6 ms) and from 8 subjects to the fast pulses (127 ± 5.6 ms), respectively. The N140 was usually embedded in a large positivity peaking at 200-300 ms.

4.1.2. Vibratory stimuli elicit bilateral P100 waves

Due to the slower rise-time of the vibratatory stimuli, most ERP deflections peaked later than those elicited by pulses. The grand-average ERPs showed that the vibratory stimuli elicited a small contralateral P50 with peak latencies 76 ms and 64 ms for the low- and high-frequency vibration, respectively.

The P50 to the low-frequency vibration was recorded as a positive deflection contralaterally only in the middle and posterior locations without clear potential reversal. Ipsilaterally, a small positive peak was seen only to the low-frequency vibration. The contralateral response to the high-frequency vibration showed a polarity reversal between the frontal and central electrode locations, whereas ipsilaterally only a negative deflection was seen. The contralateral responses were measurable in 8 subjects to the low-frequency vibration (68 ± 3.4 ms) and in 4 subjects to the high-frequency vibration (65 ± 2.2 ms). The topographical data (Fig. 2) obtained with the low frequency vibration showed a distinct contralateral P50 as a posterior positive deflection which tended to reverse its polarity in anterior records.

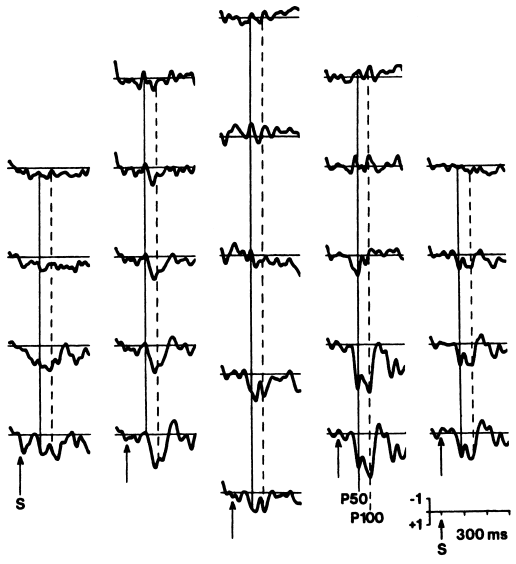

Fig. 2. *Somatosensory ERPs to 200-ms bursts of low-frequency vibration mapped from 23 locations on the scalp of a subject. The upper traces show the most frontal recording locations. The vertical solid lines are drawn at the peak latency of P50 (at 80 ms for this subject and with this stimulus type with slow onset) and the dashed lines at the P100 peak latency (130 ms). The arrows indicate stimulus onset. Data of Study I.*

A small N70 peak was seen in the grand average ERPs at the middle and posterior contralateral locations to both the low- (peak latency 92 ms) and high-frequency (peak latency 80 ms) vibration. It was seen also at the middle and contralateral locations in the topographical mapping (Fig. 2). The N70 peaks were contralaterally identified in the ERPs of 7 subjects to low-frequency (84 ± 5.6 ms) vibration and from the ERPs of 7 subjects to the high-frequency (82 ± 2.6 ms) vibration.

A bilateral positive P100 deflection was seen in the grand-average ERPs to the vibratory stimuli. In the topographical data (Fig 2), the P100 waves were also very distinct and bilateral, and for this particular subject, the contralateral P100 waves were even larger than the P50 waves. Eight subjects showed this deflection contralaterally to the low-frequency and all 10 subjects to

the high-frequency vibration. The average contralateral peak latencies were 111 ± 3.3 ms and 102 ± 3 ms, respectively. The corresponding ipsilateral latencies were 113 ± 4.2 ms and 105 ± 2.7 ms, respectively. The mean amplitude of the ipsilateral deflection was 80 % of that measured contralaterally.

The N140 was contralaterally seen in the average ERPs to the low- and high-frequency vibration. In general, the N140 was more distinct to the high- than low-frequency vibration. The 140 wave was measurable in 6 subjects to the low-frequency vibration and in 8 subjects to the high-frequency vibration. In the topographical data (Fig. 2), the N140 wave occurred posteriorly on both hemispheres and had two peaks contralaterally.

4.2. Effects of stimulus repetition on somatosensory ERPs and their MEG counterparts in humans and on intracortical responses in a monkey (Studies II, III, and Experiment 1 of Study VI)

4.2.1. The amplitudes of the scalp-recorded somatosensory ERPs decrease as a function of stimulus repetition in humans (Study VI, Experiment 1)

In this experiment, six Ss (ages 21-37; 3 females) were reading a book and ignoring stimuli delivered as trains of 4-8 successive mechanical pulses (24 Hz, 1000 µm) or vibration bursts (240 Hz; 100 µm) to the tip of the left middle finger with 1-s ISIs and with long enough (30 s) inter-train intervals (ITIs) to ascertain the recovery of ERPs between trains.

Fig. 3 shows the ERPs to the first and fourth pulse stimuli in one subject at different scalp locations. A distinct decrease in amplitudes of most deflections was obtained between the responses to the first and fourth stimuli. This diminution as a function of stimulus repetition was the most significant and the most uniform in the N140 ($F(3,20)=12.99$, $P<0.001$; for pulse stimuli, at the vertex (Cz), a one way analysis of variance (ANOVA) and P300 deflections ($F(3,20)=13.04$, $P<0.001$; for pulse stimuli, at the contralateral (C4') recording location). It was also quite distinct in the earlier P50 ($F(3,20)=4.79$, $P=0.011$; for pulses, at C4') and P100 deflections ($F(3,20)=5.51$, $P=0.006$; for pulses, at C4'). The N70, P200, and N250 were the only deflections which did not show any consistent changes with the stimulus repetition. The effects of stimulus

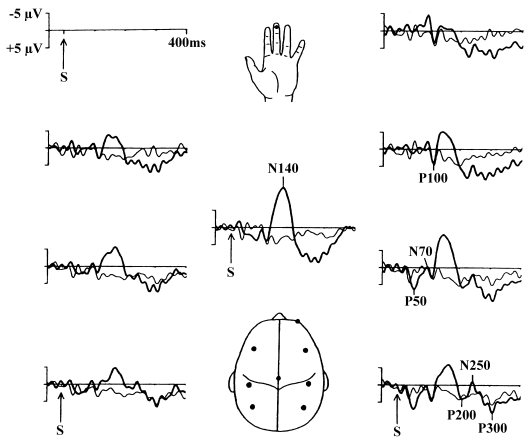

Fig. 3. *Somatosensory ERPs of a subject to tactile pulses delivered to the tip of the left middle finger, measured from different locations as indicated in the inserted head. Responses to the first and to the fourth (thin lines) stimuli in the series are shown. Data of Study VI, Experiment 1.*

repetition on the ERPs to pulses and vibrations were similar. The amplitude decrement was quite immediate (Fig. 4), occurring already between the first and second stimuli ($P<0.05$, a Duncan test, for P50, P100, and P300 at the contralateral recording locations and N140 at Cz for pulses) There were no significant changes anymore between the ERP deflections to the later (2nd-4th) stimuli.

4.2.2. Comparison of electric and magnetic evoked responses in humans (Study II)

In Study II, the stimulation paradigm was similar to in Studies VI (Experiment 1) and III, except for the electrical pulses used as stimuli instead of mechanical pulses and except for the ITI which was shorter (15 s) in Study II. Four Ss (ages 21-38, all males) participated in EEG measurements and four Ss (ages 23-38, all males) in MEG measurements; three of Ss participated in both measurements.

The electric pulses applied to the left middle finger elicited distinct P50, P100, N140, and P300 deflections. The P50 was largest at the contralateral central location and the P100 bilaterally at the frontal locations. The N140 was largest at the vertex. The P300 deflection had a wide centro-posterior distribution.

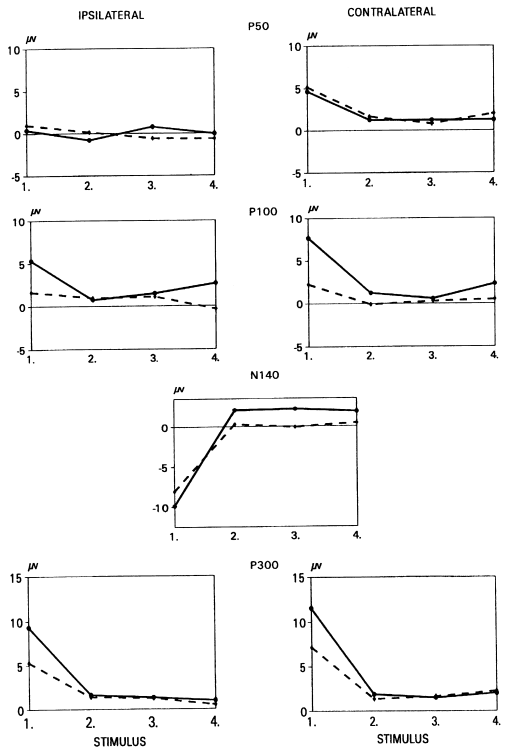

Fig. 4. *The mean amplitudes of the somatosensory P50, P100, N140, and P300 deflections of 6 subjects, measured from the contralateral (C4') and ipsilateral (C3') scalp locations and from the vertex (Cz; N140) to the repetition of 4 tactile pulses (half-cycle sinusoids of 24 Hz; continuous lines) and 4 vibratory stimuli (240 Hz; 300 ms; dashed lines) delivered to the left middle finger. Data of Study VI, Experiment I.*

The attenuation of the N140 and P300 deflection was similar as in the Study VI to the mechanical stimuli. This effect was significant for N140 at Cz ($F(3,9)=12.66$, $P<0.01$, two-way ANOVA, Factors: Repetition and Subject) and for P300 at P4' ($F(3,9)=5.37$, $P<0.05$). The change in the earlier peaks was not so clear. The overall effect of stimulus repetition was not significant for the P50 and P100 waves, although the P50 to the second stimuli was significantly diminished ($P<0.05$, Duncan test) .

Fig. 5 shows the averaged magnetic responses obtained from one subject. There were two distinct deflections, peaking at 56 ms (M50) and 114 ms (M100) to the first stimuli, probably the magnetic counterparts of the electric P50 and P100 deflections. Further, there was no difference between the M50 deflections to the first and fourth stimuli, whereas the M100 deflection to the fourth stimulus was clearly diminished .

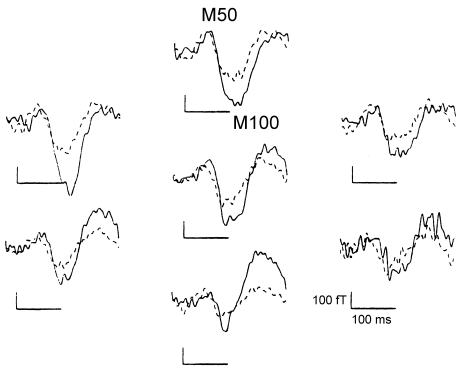

Fig. 5. *An example of magnetic responses recorded above the temporal areas of the contralateral (right) hemisphere of a subject with the 7-channel DC-SQUID magnetometer to the first (continuous lines) and last (broken lines) stimuli in the trains of 4 electrical stimuli delivered to the left middle finger. The vertical calibration lines show the time of stimulus onset. Data of Study II.*

The change of M50 as a function of stimulus repetition was not significant. A more uniform decrement was obtained for the M100 deflection. This diminution was statistically significant ($F(3,9)=6.26$, $P<0.05$). The same degree of significance was obtained for the difference between the responses to the first and second stimuli ($P<0.05$, Duncan test).

4.2.3. Intracortical somatosensory ERPs from the areas SI and SII do not diminish as a function of stimulus repetition in a monkey (Study III)

In Study III, the stimulation paradigm was the same as in Study VI, Experiment 1. At first somatosensory ERPs were recorded in six human Ss (ages 24 $\pm$ 6 years, three females) and then intracortical responses were recorded from the areas SI and SII in monkey.

Stimulus repetition attenuated the peak amplitudes of P50, P100, N140, and P300 deflection recorded at the contralteral middle scalp location in humans. This attenuation was significant ($F(3,15)$ varying between 23.6 and 89.04, $p<0.001$ for pulses and between 5.58 ($p<0.01$) and 51.4 ($p<0.001$) for vibrations; three-way ANOVA, Factors, Repetition, Attention, and Subject). There was no significant attention effect on these deflections. The largest decrements were between the first and second stimuli in a train.

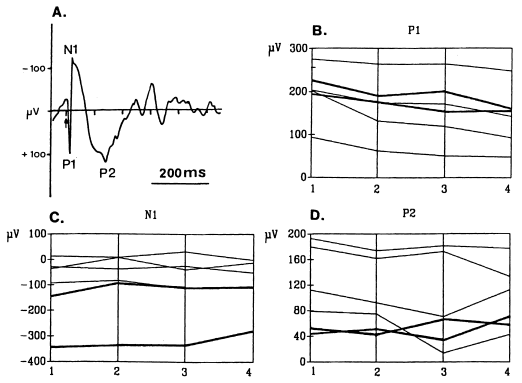

Fig. 6. *A. An intracortical somatosensory ERP to mechanical pulses to the left hand recorded from the contralateral SII of a monkey. Stimulus onset is marked with an arrow, followed by a 550 ms analysis period. B.-D. The P1, N1, and P2 amplitudes, respectively, of the responses of six cell populations as a function of the position of a stimulus in a train of four stimuli. The examples are from the SI (thick lines) and SII (thin lines) areas. Data of Study III.*

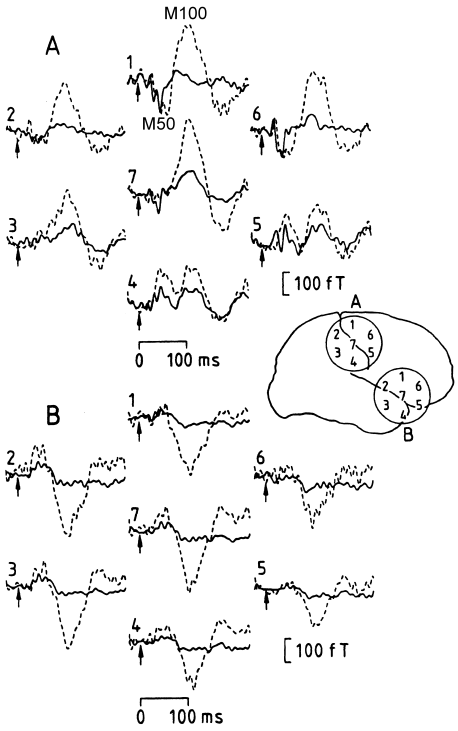

Fig. 7. *Seven-channel MEG recordings of a subject at two locations (shown schematically on the inset brain) to electric pulses presented to the left thumb (standards, continuous lines) and to the left middle finger (deviants, dashed lines). The arrows indicate the time of stimulus onset. Data of Study IV.*

Contrary to expectations, only few cell populations in SI (2 from 72) and SII (5 from 68) showed a ERP decrement as a function of stimulus repetition in the monkey (Fig. 6), when the same stimulation paradigm as that in the human experiment was used. MUA diminished as a function of repetition only in 5 recordings in SII and no in any one in SI areas. Only in one recording, both the ERP and MUA diminished with the repetition of the stimuli.

4.3. Effects of stimulus deviation on electric and magnetic evoked responses in humans (Studies IV, V, and Study VI, Experiment 2)

4.3.1. Effects of deviation in the site of electric stimuli on magnetic responses (Study IV)

In Study IV, a conventional oddball paradigm was used. Five adult Ss were instructed to count infrequent electric pulses (10 %) delivered to the left thumb (or middle finger) among the frequently presented standard stimuli (90 %) delivered to the left middle finger (or thumb), or to ignore all stimuli.

Seven-channel MEG recordings at two locations to electric pulses presented to the left thumb (standards) and middle finger (deviants) are shown in Fig. 7. The response to the standards contained main peaks at 45 and 105 ms (M50 and M100). The amplitude of the M100 was very significantly enhanced for the deviant stimuli ($P<0.005$, two-tailed t-test for pair differences). The M50 response was also larger to the deviant stimuli, but this effect was not significant. Attention increased amplitudes slightly,most clearly the M100 responses to the deviants. However, the differences did not reach statistical significance

The field patterns of these two deflections were dipolar and clearly different from each other. The M50 could be explained by the activation of the SI hand area in the posterior wall of the Rolandic fissure. During the M100 orientation of the equivalent current dipole (ECD; Hämäläinen *et al., 1993*) was different and its location agreed with the site of SII. The source locations did not differ between responses to the standards and deviants.

Additional recordings in one subject showed a similar enhancement of the M100 to the deviants even when the standards were presented to the proximal part of the middle finger and the

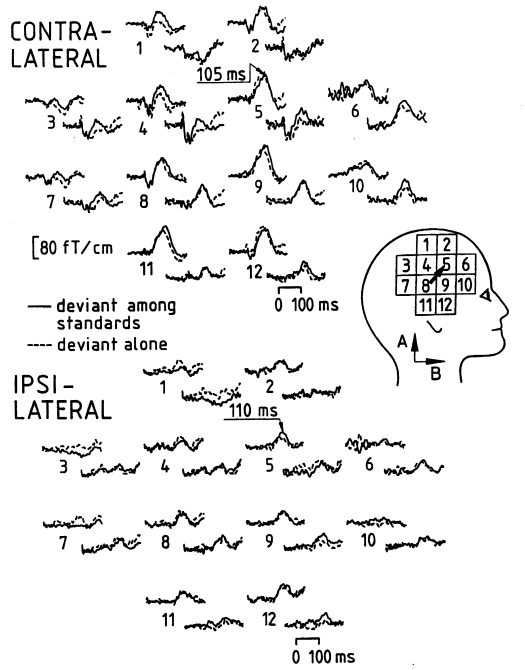

Fig 8. *MEG Responses of a subject to the deviants in the presence (continuous lines) and absence (dashed lines) of the intervening standards. The measurements were made with an 24-channel magnetometer consisting of 12 pairs of orthogonal planar gradiometers showing the largest signal above the source. In this figure, the largest signals are seen at pair 9 for the late and at pair 4 for the early deflection. For each pair of traces, the upper ones show the field gradient in the vertical direction (A on the schematic head) and the lower traces in the horizontal direction (B). The arrow in the head shows the approximate location and orientation of the equivalent source for the contralateral 100-ms response. Data of Study IV.*

deviants to the distal one, with the subject having difficulties in discriminating the stimuli.

The control recordings with the 24-channel device showed that responses to deviants presented alone, without the intervening standards, were very similar to the responses elicited by deviants among standards (Fig. 8).

4.3.2. Effects of the probability of stimulus deviation and attention on somatosensory ERPs (Study V)

In this experiment, eight Ss (ages 22-42 years, 1 male) were instructed to solve mentally arithmetic tasks and to ignore vibration bursts (30 Hz or 140 Hz) delivered to the left middle finger or to count the number of the deviants (140 Hz). The presentation probability of the standards/deviants was .85/.15, .5/.5, or 0.0/1.0 (standards omitted and the rare "deviants" presented alone with ISIs similar to the inter-deviant intervals in the .85/.15 condition).

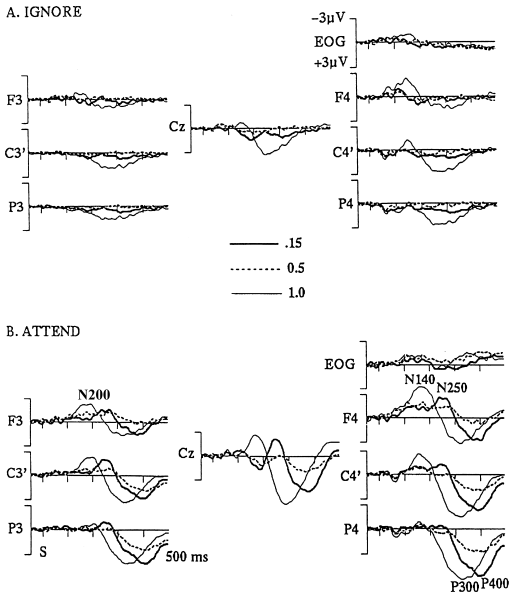

Fig. 9. *Grand-average somatosensory ERPs (8 subjects) to deviant vibratory stimuli (140 Hz, 80 μm) when deviants were infrequently (.15) presented (thick lines) among standards (30 Hz, 1000 μm), when "standards" and "deviants" were equiprobable (dashed lines), or when standards were omitted (thin lines). Subjects were solving arithmetic tasks in the ignore (A) and counting the targets in the attend condition (B). Data of Study V.*

ERPs to deviant stimuli were rather flat and quite similar in the .85/.15 and .5/.5 ignore conditions. In contrast, ERPs were different in the standard-omitted condition (0.0/1.0), including distinct N140 and P300 deflections (Fig. 9A).

In the attention conditions, there was a small N140, a prominent N250 deflection, and a marked late positive (P400) wave in ERPs to deviant stimuli when they were presented among standards (Fig. 9B). The P400 was significantly enhanced when the probability of the deviants decreased (.5 - .15) ($F(1,7)=16.46$, $P=0.0048$, two-way ANOVA; Probability and Electrodes). The N250, too, was inversely related to the probability and it occurred only in the attend conditions when the target deviants were among the standard stimuli ($F(1,7)=6.23$, $P=0.0413$. On the contrary, when subjects counted infrequently presented

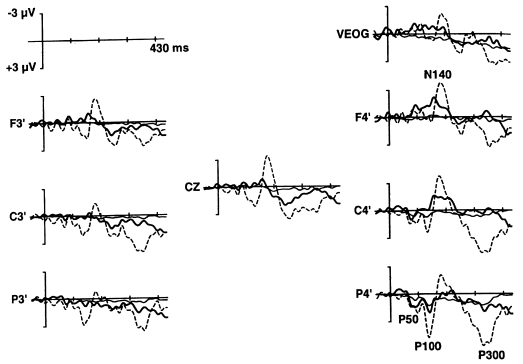

Fig. 10. *Grand-average somatosensory ERPs (8 subjects) measured from different scalp locations to vibratory stimuli (30 Hz, 1000 µm). Responses to standard stimuli (P=0.9) delivered to the tip of the left middle finger (thin lines), to deviant stimuli (P=0.1) to the tip of the thumb of the same hand (thick lines), and to 'deviant' stimuli presented alone when standards were omitted (dashed lines) are shown. Subjects were reading a book. Data of Study VI, Experiment 2.*

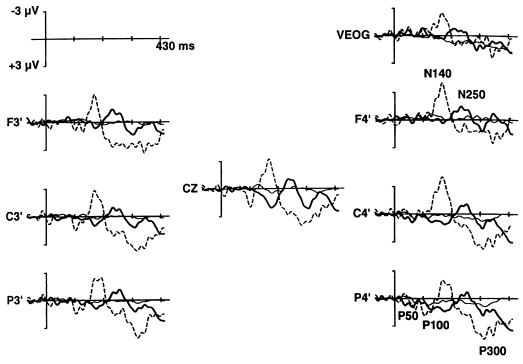

Fig. 11. *Grand-average somatosensory ERPs (8 subjects) measured from different scalp locations to vibratory stimuli delivered to the left middle finger. Responses to standard stimuli (P=0.9; 30 Hz, 1000 µm; thin lines), to deviant stimuli (P=0.1; 240 Hz, 60 µm; thick lines), and to 'deviant ' stimuli presented alone when standards were omitted (dashed lines) are shown. Subjects were reading a book. Data of Study VI, Experiment 2.*

"deviants" alone (standards omitted) the N140 and P300, with the latter clearly shortened latency (from 388 to 330 ms), were elicited, whereas no N250 wave could be found (Fig. 9B). However, there was a little 'bump' in the descending phase of N140 with a latency of about 200 ms. It was more clearly seen at the ipsilateral sites, where it was the most negative deflection and was not so much overlapped by the large N140 as at the homologous contralateral locations (Fig. 9B).

4.3.3. Deviations in the site and frequency of vibratory stimuli elicit the somatosensory mismatch negativity (Study VI, Experiment 2)

In Experiment 2 of Study VI, Ss (ages 20-31 years, 2 males) were instructed to read a book and to ignore all stimuli (standards and deviants or infrequently presented stimuli without standards). The stimulus deviance was either a change in stimulation site (thumb vs. middle finger) or in vibration frequency (30 Hz vs. 240 Hz).

Fig. 10 shows the somatosensory ERPs in the oddball condition, with standard stimuli being delivered to the left middle finger and deviant stimuli to the thumb, and also in the standards-omitted condition. All deflections (P50, P100, N140, P300) in response to deviants were larger than in response to standards, as a matter of fact, no consistently measurable components were found to standard stimuli. However, the N140 and P300 deflections were the largest to the "deviants" when the standards were omitted and then their distributions were very broad and bilateral. In contrast, the N140 distribution was quite narrow and was limited to the contralateral frontal and central areas when the deviants were presented among the standards. The amplitude of the N140 was significantly ($P<0.01$) larger to the deviants than to the standards, especially at the contralateral frontal (F4') electrode, at the latency range 118-172 ms, being most signifigant ($t(7)=-4.50$, $P=0.003$, two-tailed t-test for paired differences) at the latency of 144 ms when the deviants were delivered to the middle finger. The respective latency range ($P<0.01$) was 96-152 ms and most significant difference ($t(7)=5.79$, $P<0.001$) at the latency of 146 ms when the deviants were delivered to the thumb. In the frequency condition with the low-frequency (30 Hz) vibratory burst deviant, the respective latency range for the significant difference ($P<0.01$) was at 154-165 ms and the most significant difference ($t(7)=-4.6$, $P=0.003$) was at the latency of 161 ms. In addition, the N140 to the deviants among standards commenced earlier and was larger in amplitude at the latency range of about 100-160 ms than the N140 to the "deviants" alone. This negative deflection was quite similar in those three oddball conditions. It might be that this "extra" negativity is a somatosensory mismatch negativity. The only exception was the frequency condition in which the deviant was a high-frequency (240 Hz) vibra-

tory burst and then no negative deflection between 100 and 200 ms, instead of a broadly distributed N250 wave was found (Fig. 11).

5. DISCUSSION

In Studies I-VI reviewed here, P50 and later somatosensory ERPs, especially, P100, N140, N250, P300, and possibly a somatosensory equivalent of the auditory MMN were observed. Some other somatosensory waves, for instance N70 and P200, occurred in some Studies (e.g. I and VI) but not systematically and therefore they are not discussed here. The P50 and the somatosensory MMN are stimulus specific, with the others being endogenous unspecific responses. However, as the short-term habituation experiments (II, III, and VI) showed, even the P50 wave might include many subcomponents. Thus, the categorization of somatosensory responses is not so simple.

5.1. The fast decrease of somatosensory ERPs as a function of stimulus repetition

The amplitudes of the scalp-recorded late somatosensory ERPs (Studies II, III, and VI, Experiment 1) rapidly decreased during stimulus repetition, reaching an asymptotic level after the second stimuli in the trains. This result is consistent with those of many earlier studies (Angel *et al*., 1985; Bourbon *et al*., 1987; Callaway, 1973; Fruhstorfer, 1971; Fruhstorfer *et al*., 1970; Hari, 1980; Hari *et al*., 1979; Järvilehto *et al*., 1978; Kenemans *et al*., 1989; Loveless, 1983; Picton *et al*., 1976; Ritter *et al*., 1968; Roth and Kopell, 1969). A new finding was that the P50 and P100 waves in the human scalp-recorded ERPs also similarly diminished in amplitude (Fig. 4). The short-term decrease of this kind is usually associated to later components (Angel *et al*., 1985; Hari *et al*., 1979; Kenemans *et al*., 1989; Ritter *et al*., 1968; Roth and Kopell, 1969).

5.1.1. Stimulus-specific refractoriness?

P50 as an exegenous component should be more resistant to stimulus repetition than the later components. Some investigations have shown, however, that the direction of attention to target stimuli enhances the somatosensory P40, too (Desmedt *et al*., 1983; 1987b; Josiassen *et al*., 1982; Tomberg and Desmedt, 1996). As a matter of fact, the effect of attention has been found even in the early somatosensory P27 component, although it is an obligatory component (Desmedt and Tomberg, 1989; Garcia-Larrea *et al*., 1991). Thus, the direction of voluntary attention enhances also early the somatosensory ERPs elicited by target stimuli and consequently no early cortical components could be regarded as purely exegenous (Desmedt *et al*., 1983; Desmedt and Tomberg, 1991; Desmedt *et al*., 1987b). In addition, Tomberg et al. (1989) delivered electric stimuli to the left index and middle fingers in their continuous stimulus-presentation paradigm and found that all somatosensory early cortical components, P27, N30, and P45, except the first N20 component, are sensitive to the rate of stimulus presentation. Similar results were recently obtained also by Huttunen (1994) to electric stimuli delivered to the median nerve.

The initial decrease of P100 also was quite distinct (Studies III and VI, Experiment 1), being in a good agreement with the results of Tomberg et al. (1989), according to which P100 diminished with ISIs shorter than 1.4 s when stimuli were presented continuously. The ERP decrements for electric stimuli (Study II) were not so distinct as those for mechanical stimuli (Studies III and VI, Experiment 1), probably due to the shorter ITI. This is also true for the MEG deflections, especially for M50.

The contradiction between the fast decrement of the human scalp ERPs and the relative constancy of the cortical responses from the areas SI and SII in monkey as a function of stimulus repetition might be explained by the fact that both the scalp-recorded P50 and P100 waves include two (or more) components. One component could be sensory specific with its neural origin in SI (P50) or in SII (P100) and rather insensitive to stimulus repetition. Another component could be modality non-specific, with its neural origin in deeper and/or more widely distributed systems which are likely to be more sensitive to stimulus repetition. In the scalp-recorded ERPs, these components summate together but in the MEG recordings, mainly tangential activity from SI and SII are seen. Therefore especially the M50 would not be expected to diminish as the P50 with stimulus repetition. The stability of intracortical ERPs from areas SI and SII in the monkey is compatible with the results of Papakostopoulos and Crow (1980; cf. also Hyvärinen, 1980; 1982; Poranen and Hyvärinen, 1982). They observed that the contralateral cortical SEPs to electrical median nerve stimuli obtained from humans during surgery decreased in amplitude in the prefrontal but not in the precentral and postcentral areas as a function of stimulus repetition. Lei-

nonen et al., (1979) recorded intracortically activity of single neurons in the associative area 7 in awake monkey. They found neurons responding to touching of the contralateral arm and to visual stimuli approaching or staying near the contarlateral arm. The activity of these neurons diminished rapidly as a function of stimulus repetition. The area 7 might be a good candidate for the neural origin of the diminution of P50.

5.1.2. Nonspecific refractoriness?

The somatosensory N140 is probably analogous to the auditory N1; thus, the somatosensory N140 is probably elicited by many generators (for the generators of the auditory N1, see Näätänen, 1987). According to Näätänen (1992), the large N1 to the first stimulus is mainly due to a very large nonspecific N1 subcomponent which is not elicited by the subsequent stimuli. The specific supratemporal N1 subcomponent is also larger to the first than to the subsequent stimuli, but the diminution during stimulus repetition is not as dramatic as with the nonspecific component. The somatosensory N140 decreased similarly (Fig. 4; see also Fruhstorfer, 1971; Hari, 1980) as the auditory N1. Probably the fast decrement of the somatosensory N140 with stimulus repetition, too, is mainly due to the disappearance of a nonspecific N140 subcomponent.

The diminution of the P300 amplitude probably resulted from the strong reduction in surpriseness or temporal uncertainty of the stimulus (Donchin, 1981; Klemmer, 1956; Loveless, 1983). The P3 is attention-dependent component (Donchin *et al*., 1978). Obviously, the first "orienting" stimulus, despite the reading condition, caught attention, because it is quite difficult to ignore the first stimulus after a long "silent" period (ITI). After the long ITI, when the first stimulus was delivered, the Ss could quite well predict (because of the short constant ISIs) when the subsequent stimuli in a train will be presented and therefore these were nomore so intrusive.

As the conclusion, the initial decrease of the somatosensory deflections is caused by the disappearance of the modality nonspecific (arousal) component after the first stimulus presentation and by the stimulus-specific refractoriness. At which level the amplitude of the components remains after the first stimulus depends on the stimulus-specific refractoriness (rate effect). In other words, when using long ISIs, the diminution of the all components is caused mainly by the nonspecific refractoriness and with shorter ISIs it is (additively) caused by the nonspecific and stimulus-specific refractoriness.

Thus, it is quite probable that the large ERP amplitudes for the first stimuli are caused by neural processes related to initial orientation. The fast decrement of ERPs is mainly due to dissappearance of unspesific arousal components (N140) and to the great reduction of the time uncertainty or surpriseness (or signal value) of the stimulus (P300) after the first stimulus presentation. However, the ERP-amplitude diminution, epecially of the early components, is at least partially due to stimulus-specific refractoriness.

5.2. Somatosensory mismatch responses?

An infrequent change in the auditory stimulus stream elicits a negative deflection in ERPs at the latency of 100-200 ms after stimulus onset. Since its first description (Näätänen *et al*., 1978), this mismatch negativity has been investigated quite extensively (for reviews, see Alho, 1995; Lang *et al.*, 1995; Näätänen, 1992; Näätänen and Alho, 1995). It has been reliably recorded only for auditory stimuli. The somatosensory mismatch negativity has not been previously observed. Infrequent deviations in stimuli certainly cause changes in somatosensory ERPs, too, but these changes could be explained, for instance, by the rate effect (see Desmedt and Tomberg, 1989; 1991; Tomberg *et al*., 1989).

5.2.1. No somatosensory mismatch responses in MEG recordings

In the present MEG Study (IV), a late M100 (or P100m) response to deviant stimuli was very significantly enhanced in amplitude both in the attend and ignore oddball conditions. Infrequent electric pulses were delivered to the left thumb (or the middle finger) among frequently presented standard stimuli delivered to the middle finger (or the left thumb). The equivalent current source location of the M100 response agreed well with the site of the SII area. The control experiment showed, however, that responses to deviants alone, i.e., without standards were very similar to responses evoked by deviants among standards. This result indicated that the enhancement of the M100 response to deviant stimuli was probably not a counterpart of the somatosensory MMN but could instead be explained simply by the rate effect, for the mean ISI between the subsequent

deviants (>5 s) was much longer than that between the subsequent standards (<0.6 s).

5.2.2. Somatosensory mismatch responses in EEG recordings

In Study VI, the vibratory stimuli of different frequencies or at different skin sites were presented in the ignore oddball paradigm. The deviant stimuli, when presented alone without standards, elicited large N140 and P300 waves which were very similar to the corresponding waves elicited by the first stimulus in the short-stimulus-train paradigm. When the deviant stimulus was a high-frequency vibration burst among low-frequency bursts, it elicited a distinct N250 but no N140 wave. When the stimulus change occurred in the stimulation site or when the deviant stimulus was a low-frequency vibration burst, no N250 deflection but instead an extra negativity between 100-200 ms was observed. This negativity started earlier than did the unspecific N140, being larger at 100-160 ms. Its distribution differed from that of N140, being most clearly seen at the contralateral (right) frontal area. These data suggest separate generators for these two negativities, which is in a good agreement with results concerning the somatosensory N120 and N140 responses (García-Larrea *et al*., 1995). It is possible that the present early negativity is related to a specific sensory process: a comparison of the deviant stimulus with the memory trace of the standard stimulus as the MMN in the auditory modality. Its contralateral frontal distribution (cf.,Paavilainen *et al*., 1991) further supports interpreting this negativity in terms of a somatosensory MMN.

This result seems to be contradictory to the results of the present MEG Study (IV) where no differences were observed between the responses to the deviants among the standards and those to the deviants alone. It might be that the somatosensory MMN response is generated by a radial current dipole, and therefore it is discernible in the EEG but not in MEG recordings. Reasons for the divergent result to the high-frequency deviant stimulus are unclear but it might (as in Study IV) be due to different cortical representations of Pacinian and non-Pacinian systems (Burton and Carlson, 1986; Ferrington and Rowe, 1980; Hämäläinen *et al*., 1988; Mogilner *et al*., 1994).

5.2.3. Somatosensory ERPs to attended and unattended deviant stimuli

In the EEG Study (V) where the probability of the deviant stimuli and attention were varied, no mismatch-like response was observed to deviant vibratory stimuli in the ignore conditions. As a matter of fact, larger ERP responses were elicited by standard stimuli (30 Hz) than by deviant stimuli. This unexpected result was probably due to the unsuccessful equalization of the subjective intensities of the standard (1000 μm) and deviant (80 μm) vibratory stimuli with different frequencies (30 Hz and 140 Hz, respectively). This was done by extrapolating from previous results (see Kekoni *et al*., 1989). In addition, this result might be partially due to the different cortical representations of the Pacinian and non-Pacinian systems (Burton and Carlson, 1986; Ferrington and Rowe, 1980; Hämäläinen *et al*., 1988; Mogilner *et al*., 1994). In the ignore conditions, ERPs to the deviant stimuli were rather flat. In the attend conditions, there were small N140, distinct N250, and marked P400 waves in the ERPs to the target deviant stimuli. The N250 and P400 were maximal at the contralateral frontal (F4) and parietal (P4) sites, respectively, increasing in amplitude with the decreasing probability of the deviant stimulus. These deflections, obviously, constitute the somatosensory N2b-P3b complex. When the deviant stimuli were presented alone (standard stimuli omitted), they elicited large N140 and P300, but no N250. There was a little bump in the descending phase of the N140 which was the most clearly seen in the ipsilateral side at a latency of about 200 ms. This might be a sign of an N2b component of the ERP with a shortened latency due to the facilitation of the task, for Ss had only to detect targets instead of to discriminate between targets and non-targets. No MMN-like response was observed.

5.3. Neural origins of somatosensory ERPs

5.3.1. Somatosensory P50 is generated in the contralateral SI cortex

There is plenty of evidence that a somatosensory P50 (or P40 or P45) originates in the primary somatosensory (SI) cortex. However, its more detailed origin in SI is still rather obscure. On basis of their intracortical human recordings to electric median nerve stimuli, Allison et al. (1992) proposed that P50 is generated in the contralateral area 1 of SI cortex. The results of Desmedt and Tomberg (1989) supported this idea. In their extensive study, the distributions of the exogenous P45 and the cognition-related P40 to electric finger stimuli were similar to that of P27 originating

in the area 1 (Desmedt *et al*., 1987a). The contralateral scalp distribution of the somatosensory P50 to mechanical stimuli in Studies I and VI suggests the idea that it is a modality-specific component originating in the SI cortex. In Study I, P50 reversed its polarity approximately at the central sulcus, suggesting an origin in the posterior bank of the central fissure in area 3b. In scalp recordings, such a distinct P50-N50 potential reversal as that in the present results is rarely seen, especially when using electric stimuli (for an exception, see Desmedt and Cheron, 1980). Electric stimuli, particularly since strong stimuli eliciting motor twitches are used, activate at least the areas 3a, 3b, 1, and 2 of SI cortex, while mechanical stimuli activate mainly the area 3b in SI (Forss *et al.,* 1994). Our electrode montage might have been too coarse for permitting detailed conclusions about the origin of P50. The aforementioned interpretation is, however, concordant with the MEG study by Mogilner *et al*., (1994), in which vibratory stimuli were delivered at the upper and lower lip. In that study, the main MEG deflection occurred at 55 ms and when the dipole sources were superimposed onto corresponding MRI scans all sources located on the posterior wall of the central sulcus, within the area 3b of SI.

The present MEG responses (Study IV) to electric stimuli delivered to the thumb or to the middle finger in the oddball situation were similar to the ERP responses to mechanical stimuli (Study I). The MEG responses contained two main peaks, one at 45 and the other at 105 ms. M50 could be elicited by contralateral stimuli only. The source location of this early somatosensory evoked magnetic field (SEF) fitted well the site of SI, being in agreement with the early studies (Brenner *et al*., 1978; Hari *et al*., 1984; Huttunen *et al*., 1987; Okada *et al*., 1984) and also with the more recent somatosensory MEG studies according to which only SI sources are active at 20-70 ms (Forss *et al*., 1994a; 1994b; 1995; Hari *et al*., 1993; Mauguière *et al*., 1997a; Mogilner *et al*., 1994).

5.3.2. Somatosensory P100 is bilaterally generated in the SII cortices

The origin of the somatosensory P100 component, first described by Desmedt and Robertson (1977), is not as distinct as that of the preceding P50. P100 is an attention-dependent component, being clearly enhanced to target stimuli (Desmedt *et al*., 1983). Its scalp distribution is rather broad and bilateral, being most prominent at the posterior scalp areas (Desmedt and Tomberg, 1989; Desmedt *et al*., 1987b). The P100 distribution (Study I) was quite similar to that observed in the afore-mentioned (Desmedt and Tomberg, 1989; Desmedt *et al*., 1987b) studies. In addition, the peak of P100 was larger and earlier at the contralateral than ipsilateral scalp locations (see Figs. 1 and 2), so was also the magnetic response M100 (Study IV). Hari et al. (1983) found an MEG response to electric stimuli at the median nerve at latencies 95-125 ms. The field distribution was in agreement with sources on the upper bank of the Sylvian fissure, in the area of SII cortex. This finding was confirmed by many subsequent studies (Forss *et al*., 1994a; 1994b; 1995; 1996; Hari *et al*., 1993; 1984; Mauguière *et al*., 1997a). The results of intracortical recordings in humans also support the origin of P100 component in the SII areas (Allison *et al*., 1989b; 1992). The source location of the M100 Study (IV) matched well the approximated location of SII, too. In addition, the present data suggest that SII contains accurate finger representations since the responses to the stimulation of one finger was not significantly affected by the intervening stimuli delivered to the other finger (Fig. 8).

5.3.3. Somatosensory N140 includes many subcomponents

The somatosensory N140 (Desmedt and Robertson, 1977) is probably analogous to the auditory N1 which includes many subcomponents, both exegenous and endogenous nature (e.g. Näätänen and Picton, 1987). The N140 is highly sensitive to experimental conditions. The peak latency of somatosensory N140 widely varied in different studies, one possible reason for this large variation being that different components are measured in different studies. The neural generators of the somatosensory N140 are incompletely known. On the basis of their topographic scalp mapping data Desmedt et al. (1989) proposed that N140 is generated by sequential processes by postrolandic, posterior parietal, and prefrontal structures, including areas 7b and 46. According to García-Larrea et al. (1995), there are two somatosensory negative components in the 100-150 ms latency range, an N120 and the later N140 response. The N120 response to standard stimuli occurred in all, neutral, unattended-hand, attended-hand, oddball conditions. It was not sensitive to spatial attention. The amplitudes of N120 were almost the same, regardless of whether the standards being attended or ignored. On the contrary, the N140 was highly sensitive to spatial attention, disappearing altogether in the neutral condition. The distribution of the exogenous

N120 was highly lateralized, being most prominent over the contralateral temporal scalp area, consistently with its generation in the SII area. This was concordant with the intracortical recordings in the suprasylvian regions in humans by Allison et al. (1992). The distribution of N140 overlapped with that of N120 in the unattended- and attended-hand conditions. It was bilateral but contaralaterally preponderant. The endogenous N140 was the most prominent and the most widely distributed in the attended-hand conditions and totally disappeared in the neutral (no task) condition. García-Larrea et al. (1995) did not propose any neural generator for this somatosensory processing negativity (PN) (cf. Näätänen *et al*., 1978; Näätänen and Michie, 1979). The present somatosensory ERP data (Study I) confirm the idea of two components in that the N140 occurred with two peaks in some recordings. The experimental condition, however, was 'neutral' in Study I and thus did not enable one to differentiate these exegenous and endogenous negativities.

Hari et al. (1993) observed MEG responses to electric stimuli delivered to the left thumb. The locations of the ECDs at peak latencies 45 and 145 ms fitted well to SI and at the latency of 115 ms to SII cortices. Forss et al. (1994b) explained MEG responses to electric stimuli delivered to the left and right median nerves with a 4-dipole model. They explained the early responses by activation of the SI hand area and middle-latency responses at 70-110 ms by that of the contra- and ipsilateral SII areas. At about the same latency of the middle-latency responses, they found an additional source in the contralateral parietal cortex, posterior and medial to the SI hand area, its more exact locus being probably in the wall of the postcentral sulcus. Forss et al. (1994a) obtained quite similar results to airpuffs, too. In that study, the airpuffs activated the posterior parietal source only in the right hemisphere (quite an interesting connection to the neglect syndrome). Further, Forss et al. (1996) found an additional source of the cortical activation elicited by ulnar and median stimuli. This response was observed at 120-160 ms. It was clearly enhanced by attention and was generated in the mesial cortex of the paracentral lobule, probably originating in the area 4 of the motor cortex but the posterior supplementary motor area was not ruled out. In addition, Mauguière et al. (1997a) found contralateral and ipsilateral frontal activation to median nerve stimuli at 110-170 ms. The frontal ECDs were located anteriorly to the precentral sulcus in the midfrontal or inferior frontal gyri (cf. Desmedt and Tomberg, 1989). At short ISIs (1.2 s), attention had no effect on the activity of ECD sources elicited when electric stimuli delivered to the left median nerve were infrequently (15 %) omitted or replaced by an ulnar nerve stimulus (omission/deviation interval 2.4-21.6 s) (Mauguière *et al*., 1997b). On the contrary, when the 'deviant' median nerve stimuli were presented alone with the same irregular ISIs (2.4-21.6 s), all ECD sources (contralateral SI, contra- and ipsilateral parietal opercular, contralateral posterior parietal, and contra- and ipsilateral frontal sources) were clearly strengthened. When Ss counted these 'deviants' the ECDs were further enhanced, except those in SI (cf. Hyvärinen, 1980; 1982; Poranen and Hyvärinen, 1982). This attention effect was the most marked in the ipsilateral SII area and in both frontal areas. According to Mauguière et al. (Mauguière *et al*., 1997b), their results strongly suggest that the ipsilateral parietal opercular cortex, and presumably the prefrontal cortex on both hemispheres, participate in the vertex ERP culminating at a latency of 140-150 ms.

5.3.4. Origin of the somatosensory mismatch negativity

In the auditory system, any supraliminal change in a continuous stream of stimuli elicits a negative shift, the mismatch negativity (Näätänen *et al*., 1978), overlapping the auditory N1 component. The auditory MMN has (at least) two components (Deouell *et al*., 1998; Giard *et al*., 1990; Näätänen and Michie, 1979), a bilateral sensory-specific one generated in the supratemporal auditory areas, and a frontal one which is preponderant in the right hemisphere and is associated with involuntary attention switch (Paavilainen *et al*., 1991).

The origin of a possible somatosensory MMN is unknown, but it was the most marked at the contralateral (right) frontal electrode (e.g. Fig. 10) being concordant with the results of the auditory MMN (e.g. Paavilainen *et al*., 1991). The role of the different hemispheres of the present MMN kind of responses is not known, however, because the stimuli were delivered only to the left hand. The mismatch process requires accurate sensory information, and in this sense the SI area would be a good candidate for the neural origin of the somatosensory mismatch negativity. Another excellent candidate would be the SII area. The results of Study IV and the more recent results of (Hari *et al*., 1993) showed that the SII contains quite accurate finger representations. In addition, Hari et al. (1993) showed that the recovery cycle of the SII response is about the same as the duration of the sensory-memory trace (10 s) in the auditory system (Lu *et al*., 1992; Sams *et al*.,

1993). According to García-Larrea *et al*. (1995), the somatosensory N120 is generated in the contra- and ipsilateral SII areas. It was specific, exegenous, and insensitive to changes in attention - properties which are usually associated to the auditory MMN. It may be that this generator participates in the somatosensory mismatch processing. It could be that all these areas, SI, SII, and the frontal areas, participate in somatosensory change detection. The auditory MMN reflects a complex pattern of generators (Alho, 1995; Deouell *et al*., 1998; Giard *et al*., 1990; see also Halgren *et al*., 1998), and probably the same is true in the somatosensory system. At this stage, however, it is not possible to locate with any certainty the somatosensory MMN. Accurate localization would require new studies with dense eletrode montages combined with some modern imaging technique e.g., fMRI (functional Magnetic Resonance Imaging) or PET (Positron Emission Tomography).

5.3.5. Origins of the late N2 and P3 waves

In active oddball or discrimination conditions, infrequent deviant or target auditory stimuli elicit N2b and P3b components. Both have bilateral broad central scalp distributions with central and centroparietal amplitude maxima. These two components have different generators although they usually occur together. Temporal parietal lesions in humans reduce or abolish somatosensory, auditory, and visual target P3 (P3b) and novelty P3 (P3a) waves but do not affect N2 waves (Knight, 1990a; Knight *et al*., 1989; Yamaguchi and Knight, 1991; 1992). However, lesions in the upper parietal areas, in the rostral inferior and superior parietal lobes reduce the auditory target N2 with no effect on P3b (Knight *et al*., 1989). Prefontal lesions reduce P3a and abolish its habituation with stimulus repetition but does not have an influence on the target N2-P3 (Knight, 1984; 1990a; Yamaguchi and Knight, 1991). Hippocampal lesions had similar effects on the auditory and somatosensory ERPs and, in addition, reduced sympathetic skin response and flattened its habituation (Knight, 1996). According to Knight (1996), the hippocampal region plays a crucial role in the limbic-cortical network that detects, and responds to, novel stimuli. However, according Alho et al. (1998), the auditory cortex in the superior temporal plane is also involved in the neural network of involuntary attention switching to the novel auditory stimuli.

On the basis of the intracerebral recordings in humans, Halgren et al. (1995a, 1995b) propose that N2b/P3b generators are located in the medial temporal lobe, especially in the hippocampus (P3b) and possibly in the rhinal cortex (N2b) and in the multimodal association cortex, possibly including the superior parietal lobule (N2b). Kropotov et al. (1995) recorded N2/P3 waves to auditory and visual stimuli in active oddball conditions from many cerebral structures, for example from parietal cortex (the junction of areas 40 and 43), from frontal cortex (areas 4, 6, 8, and 32), from anterior cingulate cortex, and from hippocampus. In their recent work, Halgren et al. (1998) summarize their previous results (Baudena *et al*., 1995; Halgren *et al*., 1995a; 1995b; Smith *et al*., 1990; Stapleton and Halgren, 1987), involving the generators of the late cognitive potentials in auditory and visual cognitive tasks. According to these authors, the P3a system is activated by rare auditory or visual stimuli, regardless of whether they are targets or non-targets (resulting in the elicitation of the N2a/P3a/SW complex). The P3a is generated in the fronto-parieto-cingulate system, which has been associated with the orientation of attention, including the dorsolateral prefontal cortex (area 46), the supramarginal gyrus (area 40), and the cingulate gyrus. Whenever the scalp-recorded P3 wave is elicited by a stimulus, it activates the P3a system and, further if it is a target (attended) stimulus, it activates the "P3b event encoding system", too. The P3b is generated in the hippocampus, the superior temporal sulcus, the ventrolateral prefrontal cortex, and in the intraparietal sulcus. This depth P3b is modality non-specific and is associated with modality non-specific N2b probably generated in the rhinal cortex. Knight et al's. (1989) results showed, however, that the rostral inferior parietal lobe and portions of the superior parietal lobe (area 7) could participate in the generation of the N2b, too.

In Study V, the somatosensory N250 and P400 (or P300) to mechanical stimuli in the attend conditions were broadly and bilaterally distributed and were preponderant on the contralateral scalp, which is concordant with the previous literature (e.g., Bruyant *et al*., 1993; Ito *et al*., 1992; Josiassen *et al*., 1982; Kujala *et al*., 1995). It is here proposed that these waves represent the somatosensory N2b-P3b complex. However, the coarse electrode montage used in the present study does not provide the basis for the accurate localization of their generators.

6. CONCLUSIONS

1. In the neutral ignore condition the mechanical stimuli elicited somatosensory ERPs in which P50 and P100 waves were the most marked deflections. The P50 was largest over the scalp contralateral to the stimulated skin area and it reversed its polarity approximately at the central sulcus, confirming that it is a specific component and generated in the SI cortex, probably in area 3b. The P100 was broadly and bilaterally distributed. Its distribution confirmed the idea that it is probably generated in the SII cortices. The N140 was rather small in amplitude, obviously because of the rate effect. The N140 had two peaks on the contralateral side, suggesting that there are two components (N120 and N140) at this latency range.

2. The late nonspecific N140 and P300 waves to mechanical stimuli diminished in amplitude as a function of repetition, rapidly reaching an asymptotic low level as soon as after the first or second stimulus. In addition, the P50 and P100 amplitudes attenuated almost equally rapidly with stimulus repetition.

3. The electric P50, P100, N140, P300, and also the magnetic M50 and M100 amplitudes decreased as a function of stimulus repetition when electric pulses were used as stimuli. However, this diminution was not so distinct as with mechanical stimuli, especially the decrease of the M50 amplitude was not so marked. This was possibly partially due to the shorter ITI (30 s vs. 15 s).

4. No marked response decrement was observed when somatosensory ERPs to mechanical stimuli were directly recorded from the SI and SII areas in a monkey, suggesting that the response decrements mentioned in (2) originate elsewhere. Probably, the response enhancement to the first stimulus can be assimilated with the nonspecific orientation (arousal) effect, the fast response decrease being mainly due to the rapid disappearance of this effect with stimulus repetition.

5. In the oddball paradigm, MEG responses to deviant electric stimuli were significantly enhanced . However, the responses to ‘deviants’ alone were quite similar to the responses to deviants among standards, suggesting that this MEG response enhancement was not generated by the mismatch process but could rather be explained by the rate effect.

6. In active oddball conditions, deviant target stimuli elicited an N250-P300 complex, which is obviously the somatosensory N2b-P3b complex, and probably related to deviance discrimination or target detection.

7. In the ignore oddball conditions, when there was a change in the stimulus location or in the frequency of vibratory stimuli (from higher to lower), then an extra negativity succeeding by the N140 was observed which is probably the somatosensory analogy to the well-established auditory MMN, suggesting a sensory memory mechanism involved in mismatch processing in somatosensory modality.

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PROCESSING OF STIMULUS REPETITION AND CHANGE IN THE SOMATOSENSORY SYSTEM: RECORDINGS OF ELECTRICAL AND MAGNETIC BRAIN RESPONSES

Doctoral Dissertation

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Academic dissertation to be publicly discussed, by due permission of the Faculty of Arts at the University of Helsinki in auditorium XII, on the 29th of January, 1999, at 12 o'clock

Original Publications

LIST OF PUBLICATIONS

I. Hämäläinen, H., Kekoni, J., Sams, M., Reinikainen, K. and Näätänen, R. (1990) Human somatosensory evoked potentials to mechanical pulses and vibration: contributions of SI and SII somatosensory cortices to P50 and P100 components. *Electroencephalography and clinical Neurophysiology,* 75: 13-21.

II. Kekoni, J., Tiihonen, J. and Hämäläinen, H. (1992) Fast decrement with stimulus repetition in ERPs generated by neuronal systems involving somatosensory SI and SII cortices: electrical and magnetic evoked response recordings in humans. *International Journal of Psychophysiology,* 12: 281-288.

III. Hämäläinen, H., Kekoni, J., Gröhn, J., Läh-teenmäki, A., Reinikainen, K. and Näätänen, R. (1990) Decrement of human somatosensory evoked potentials with stimulus repetition: Comparison with cortical responses in monkey. In C.H.M.Brunia, A.W.K.Gaillard and A.Kok (Eds.), *Psychophysiological Brain Research,* Tilburg Univ. Press, pp. 40-45.

IV. Hari, R., Hämäläinen, H., Hämäläinen, M., Kekoni, J., Sams, M. and Tiihonen, J. (1990) Separate finger representations at the human second somatosensory cortex. *Neuroscience,* 37: 245-249.

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VI. Kekoni, J., Hämäläinen, H., Saarinen, M., Gröhn, J., Reinikainen, K., Lehtokoski, A. and Näätänen, R. (1997) Rate effect and mismatch responses in the somatosensory system: ERP-recordings in humans. *Biological Psychology,* 46: 125-142.